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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,176	03/12/2001	Sean Ekins	PC10697A	1034

7590 12/07/2004

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 12/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,176	EKINS, SEAN	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004 and 25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *16-22,24,27-33,41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15,23,25,26,34-40 and 43* is/are rejected.

7)☐ Claim(s) *3,14,15,26 and 38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/03, 9/16/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. For the purpose of examination, step (ii) of claim 1 is interpreted to require correlation of compounds in a training set database with experimentally determined CYP2D6 inhibitory potency.

Election/Restrictions

2. Applicant's election of Group 1 and training compound species of (d,l)-2-methoxy-4,5-methylenedioxyamphetamine and optimum fit method species of partial least squares technique in the replies filed on 21 June 2004 and 25 October 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 16-22, 24, 27-33, 41, and 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on 21 June 2004 and 25 October 2004.

Drawings

4. The drawings were received on 25 October 2004. These drawings are accepted.

Specification

5. The abstract of the disclosure is objected to because it exceeds 150 words in length Correction is required. See MPEP § 608.01(b).

Claim Objections

6. Claims 14, 15, and 38 are objected to because of the following informalities: Claim 14 recites "an" in line 1 and claim 38 recites "an" in line 3 and should be amended to recite "a." Appropriate correction is required.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 23, 25, 26, and 39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to data or data that is entirely non-functional descriptive material on computer readable media. See MPEP 2106.

Allowable Subject Matter

8. Claims 3 and 26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 1, 2, 4-6, 10, 11, 13-15, 23, 25, 39, 40, and 43 are rejected under 35 U.S.C. 102(a) as being anticipated by Ekins et al. (Pharmacogenetics Vol. 9, pages 77-489 (1999) (cited in the Information Disclosure Statement filed 16 September 2002)).

The claims are drawn to a method of making a phramacophore of an inhibitor of cytochrome protein CYP2D6. The training set of inhibitors includes 5 or more selective serotonin reuptake inhibitors (SSRI). Multiple conformations of each training set molecule is considered and one or more pharmacophores are generated with multiple chemical property features. The lowest cost (best fit) pharmacophore is selected. In some embodiments the claims are drawn to pharmacophore models produced by the method or computers and computer readable media comprising the pharmacophore models produced by the method. In some embodiments the SSRI compounds span three orders of magnitude with respect to K_i, the observed K_i is between 0.1 micromolar to 100 micromolar, the number of conformers is 255, the training set comprises at least 14 compounds, and at least 10 pharmacophores are generated. In some embodiments the pharmacophore is used to determine the CYP2D6 inhibitory potential of an SSRI compound by fitting the compound to the pharmacophore by a least squares technique.

Ekins et al. shows in the abstract and throughout a method of making a pharmacophore of inhibitors of CYP2D6. Table 1 shows some members of a training set that includes multiple SSRI compounds with K_i values ranging from 0.03 to 529.51. On page 479 Ekins et al. details a computer mediated method of making a pharmacophore in which multiple conformations of each inhibitor are considered, a maximum of 255 conformers were considered for each inhibitor, ten pharmacophores were generated for each inhibitor, the pharmacophores have multiple chemical

property features, and the lowest cost pharmacophore is selected. Ekins et al. shows use of a partial least squares technique on pages 482-484 to fit SSRI molecules to the data.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 1, 7-9, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al.

The claims are drawn to a method of making a phramacophore of an inhibitor of cytochrome protein CYP2D6. The training set of inhibitors includes 5 or more selective serotonin reuptake inhibitors (SSRI). Multiple conformations of each training set molecule is considered and one or more pharmacophores are generated with multiple chemical property features. In some embodiments the energy range of the conformers is either 10, 35, or 50 Kcal/mole. Claim 38 is drawn to a method of making a pharmacophore of SSRI inhibitors with a K_i of 10 micromolar or greater for CYP2D6.

Ekins et al. shows in the abstract and throughout a method of making a pharmacophore of inhibitors of CYP2D6. Table 1 shows some members of a training set that includes multiple SSRI compounds with K_i values ranging from 0.03 to 529.51. On page 479 Ekins et al. details a computer mediated method of making a pharmacophore in which multiple conformations of each inhibitor are considered. Ekins et al. shows conformers with an energy range of 20 Kcal/mole were used. Ekins et al. does not show an energy range of conformers of either 10, 35, or 50 Kcal/mole. Ekins et al. states on page 478 that CYP2D6 is involved in the metabolism of many drugs and that it is desirable that new drugs not inhibit the activity of CYP2D6. Ekins et al. does not show pharmacophore training set drugs that do not have a K_i of less than 10 micromolar.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the energy range of conformers of Ekins et al. to include either 10, 35, or 50 Kcal/mole because Ekins et al. shows use of an energy range of 20 Kcal/mole and extension of the range of conformers in either direction from that used by Ekins et al. would be routine to one of ordinary skill in the art for the purpose of consideration of additional conformers in the method of Ekins et al. It would have been further obvious to use a training set of molecules that are SSRI compounds with a K_i of greater than 10 micromolar towards CYP2D6 so that the pharmacophore could be used to design drugs that are not strong inhibitors of CYP2D6 to avoid interference with the many other drugs that CYP2D6 metabolizes as pointed out by Ekins et al. on page 478.

14. Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al. in view of Wu et al. (Biochemical Pharmacology Vol. 53, pages 1605-1612 (1997) (cited in the Information Disclosure Statement filed 16 September 2002)).

The claims are drawn to a method of making a phramacophore of an inhibitor of cytochrome protein CYP2D6. The training set of inhibitors includes 5 or more selective serotonin reuptake inhibitors (SSRI). Multiple conformations of each training set molecule is considered and one or more pharmacophores are generated with multiple chemical property features. In one embodiment one of the training inhibitor molecules is (d,l)-2-methoxy-4,5-methylenedioxyamphetamine.

Ekins et al. shows in the abstract and throughout a method of making a pharmacophore of inhibitors of CYP2D6. Table 1 shows some members of a training set that includes multiple SSRI compounds with K_i values ranging from 0.03 to 529.51. On page 479 Ekins et al. details a computer mediated method of making a pharmacophore in which multiple conformations of each inhibitor are considered. Ekins et al. does not show a training inhibitor molecule that is (d,l)-2-methoxy-4,5-methylenedioxyamphetamine.

Wu et al. shows that (d,l)-2-methoxy-4,5-methylenedioxyamphetamine is a potent inhibitor of CYP2D6 on page 1607 in Table 1 with a K_i of 0.17.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use (d,l)-2-methoxy-4,5-methylenedioxyamphetamine as one of the training molecules of a pharmacophore of CYP2D6 inhibitors because Wu et al. shows that (d,l)-2-methoxy-4,5-methylenedioxyamphetamine is a potent inhibitor of CYP2D6.

15. Claims 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al. in view of Rogers et al.

The claims are drawn to a method of using a pharmacophore of an SSRI inhibitor of cytochrome protein CYP2D6 to design SSRI molecules that do not inhibit CYP2D6 by use of

testing of randomly generated variant molecular structures. In some embodiments the K_i is 1-100 micromolar.

Ekins et al. shows in the abstract and throughout a method of making a pharmacophore of inhibitors of CYP2D6. Table 1 shows some members of a training set that includes multiple SSRI compounds with K_i values ranging from 0.03 to 529.51. Ekins et al. does not show use of testing of randomly generated variant molecular structures. Ekins et al. states on page 478 that CYP2D6 is involved in the metabolism of many drugs and that it is desirable that new drugs not inhibit the activity of CYP2D6. Ekins et al. does not show a pharmacophore of drugs that have a K_i of 1 micromolar or greater.

Rogers et al. shows a method of using a genetic algorithm to produce and test recombined variants of structures in a QSAR model to produce structures with improved functions in the abstract and in several working examples on pages 857-865. Rogers et al. concludes on page 864 that employing a genetic algorithm allows for determination of structures with desired properties due to discovery of combinations of basis functions that take advantage of correlations only available in combination.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Ekins et al. by use of the genetic algorithm of Rogers et al. because Rogers et al. shows that use of a genetic algorithm allows for generation of recombinant structures with improved propertied. It would have been further obvious to use a training set of molecules that are SSRI compounds with a K_i of greater than 1 micromolar towards CYP2D6 so that the pharmacophore could be used to design drugs that are not strong

inhibitors of CYP2D6 to avoid interference with the many other drugs that CYP2D6 metabolizes as pointed out by Ekins et al. on page 478.

16. Claims 1, 2, 4-11, 13-15, 23, 25, 38, 39, 40, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strobl et al. (J. Med. Chem. vol. 36, pages 1136-1145 (1993) cited in the Information Disclosure Statement filed 16 September 2002) in view of Lane in view of Hopfinger et al.

The claims are drawn to a method of making a phramacophore of an inhibitor of cytochrome protein CYP2D6. The training set of inhibitors includes 5 or more selective serotonin reuptake inhibitors (SSRI). Multiple conformations of each training set molecule is considered and one or more pharmacophores are generated with multiple chemical property features. The lowest cost (best fit) pharmacophore is selected. In some embodiments the claims are drawn to pharmacophore models produced by the method or computers and computer readable media comprising the pharmacophore models produced by the method. In some embodiments the SSRI compounds span three orders of magnitude with respect to K_i, the observed K_i is between 0.1 micromolar to 100 micromolar, the number of conformers is 255, the training set comprises at least 14 compounds, and at least 10 pharmacophores are generated. In some embodiments the pharmacophore is used to determine the CYP2D6 inhibitory potential of an SSRI compound by fitting the compound to the pharmacophore by a least squares technique. Claim 38 is drawn to a method of making a pharmacophore of SSRI inhibitors with a K_i of 10 micromolar or greater for CYP2D6.

Strobl et al. shows in the abstract and throughout a pharmacophore of inhibitors to CYP2D6. Strobl et al. shows that multiple conformers of the training set molecules with an

energy limit of up to 50 kcal/mol were used on page 1137. Strobl et al. shows a training set in Table 1 of 6 molecules with a K_i of from 0.0057 to 25, a greater than three order of magnitude range. Strobl et al. does not show a training set of inhibitors of 5 or more SSRI molecules, generation of multiple preliminary pharmacophores or selection of the best fit pharmacophore, examination of 255 conformers, or prediction of K_i by use of the pharmacophore, or a pharmacophore of K_i of 10 micromolar or greater for CYP2D6.

Lane shows on pages 37-43 that many SSRI drugs inhibit CYP2D6 and can cause clinical problems due to interactions with metabolism of other drugs. In Table 5, Lane shows SSRI molecules with a wide range of inhibitory strengths.

Hopfinger et al. reviews 4D-QSAR methods. Hopfinger et al. shows on pages 10510-10512 and Table 1 a ten step method of development of a QSAR model. The method comprises iteratively constructing pharmacophores based on multiple conformers of the training set molecules, and selecting the lowest energy model. Hopfinger et al. shows in Table 3 the pharmacophore chemical properties. Hopfinger et al. shows an example on page 10517 that examines 40,000 conformers. Hopfinger et al. show use of partial least squares analysis in step 6 of table 1, and compares predicted and experimental activities of a working example in figure 10.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Strobl et al. by use of a training set of SSRI inhibitors because Lane shows SSRI compounds and that they inhibit CYP2D6 and cause drug interaction effects. It would have been further obvious to use a training set of molecules that are SSRI compounds with a K_i of greater than 10 micromolar towards CYP2D6 so that the pharmacophore could be used to design drugs that are not strong inhibitors of CYP2D6 to avoid

interference with the many other drugs that CYP2D6 metabolizes as pointed out by Lane. It would have been further obvious to use the 4D-QSAR method of Hopfinger et al. because Hopfinger et al. shows that their method allows for consideration of many conformers of the training set molecules in development of a pharmacophore or QSAR model. It would have been obvious to increase the number of compounds in the training set to improve sampling of inhibitor structures and to use 255 conformers because Hopfinger et al. shows that examination of a large number of conformers by 4D-QSAR produces useful model results.

17. Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strobl et al. in view of Lane in view of Hopfinger et al. as applied to claims 1, 2, 4-11, 13-15, 23, 25, 38, 39, 40, and 43 above, and further in view of Wu et al.

The claims are drawn to a method of making a pharmacophore using a training set that includes (d,l)-2-methoxy-4,5-methylenedioxyamphetamine.

Strobl et al. in view of Lane in view of Hopfinger et al. as applied to claims 1, 2, 4-11, 13-15, 23, 25, 38, 39, 40, and 43above does not show a training set that includes (d,l)-2-methoxy-4,5-methylenedioxyamphetamine.

Wu et al. shows that (d,l)-2-methoxy-4,5-methylenedioxyamphetamine is a potent inhibitor of CYP2D6 on page 1607 in Table 1 with a K_i of 0.17.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Strobl et al. in view of Lane in view of Hopfinger et al. as applied to claims 1, 2, 4-11, 13-15, 23, 25, 38, 39, 40, and 43 above to use (d,l)-2-methoxy-4,5-methylenedioxyamphetamine as one of the training molecules of a pharmacophore

of CYP2D6 inhibitors because Wu et al. shows that (d,l)-2-methoxy-4,5-methylenedioxyamphetamine is a potent inhibitor of CYP2D6.

18. Claims 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strobl et al. in view of Lane in view of Hopfinger et al. as applied to claims 1, 2, 4-11, 13-15, 23, 25, 38, 39, 40, and 43 above, and further in view of Rogers et al.

The claims are drawn to a method of using a pharmacophore of an SSRI inhibitor of cytochrome protein CYP2D6 to design SSRI molecules that do not inhibit CYP2D6 by use of testing of randomly generated variant molecular structures. In some embodiments the K_i is 1-100 micromolar.

Strobl et al. in view of Lane in view of Hopfinger et al. as applied to claims 1, 2, 4-11, 13-15, 23, 25, 38, 39, 40, and 43 above does not show a pharmacophore of drugs that have a K_i of 1 micromolar or greater.

Rogers et al. shows a method of using a genetic algorithm to produce and test recombined variants of structures in a QSAR model to produce structures with improved functions in the abstract and in several working examples on pages 857-865. Rogers et al. concludes on page 864 that employing a genetic algorithm allows for determination of structures with desired properties due to discovery of combinations of basis functions that take advantage of correlations only available in combination.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Strobl et al. in view of Lane in view of Hopfinger et al. as applied to claims 1, 2, 4-11, 13-15, 23, 25, 38, 39, 40, and 43 above by use of the genetic algorithm of Rogers et al. because Rogers et al. shows that use of a genetic algorithm allows for

generation of recombinant structures with improved propertied. It would have been further obvious to use a training set of molecules that are SSRI compounds with a K_i of greater than 1 micromolar towards CYP2D6 so that the pharmacophore could be used to design drugs that are not strong inhibitors of CYP2D6 to avoid interference with the many other drugs that CYP2D6 metabolizes as pointed out by Lane.

Conclusion

19. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center at (800) 786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.S. Brusca 4 December 2004

John S. Brusca
Primary Examiner
Art Unit 1631

jsb